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EXAMINER	
HELMS, LARRY RONALD	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,639	BRODIN ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *17-33,35,36 and 38-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,34 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/22/03,3/20/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-16, 34, 37, in the paper filed 9/15/04 is acknowledged. The traversal is on the ground(s) that the inventions of Groups I to XX are closely related and that a proper search of any of the claims should, by necessity, require a proper search of the others and Groups I to XX share the special technical feature of relating to gastrointestinal epithelial cells and malignant diseases of the same. This is not persuasive. Applicant has provided no evidence to establish why the requirement for restriction is improper. Although the response states that the special technical feature is gastrointestinal epithelial cells and malignant diseases of the same, the claims are drawn to different products and methods not cells and as stated in the restriction requirement, the technical feature recited in claim 1 is not special because claim 1 recites an antibody and all of the claims are not directed to an antibody. As to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

2. Claims 17-33, 35-36, 38-57 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/15/04.

3. Claims 1-16, 34, 37 are under examination.

Claim Objections

4. Claim 37 is objected to because of the following informalities: It appears as though "vaccin" in the claim is spelled wrong and should be "vaccine". Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-16, 34, 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-16, 34, 37 are indefinite for reciting "derivative" in claims 1, 4 because the exact meaning of the term is unclear. The term "derivative" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of an ascertainable meaning for said phrase. Since it is unclear how the antibodies are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear whether the "derivative" of the

antibody is formed by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence, for examples. In addition, since the term "derivative" does not appear to be clearly defined in the specification, and the term can encompass proteins with amino acid substitutions, insertions, or deletions, antibody fragments, chemically derivatized molecules, or even antibody mimetics. In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

b. Claim 2 is indefinite for reciting "sequences are of Macaca fascicularis origin" because it is unclear if the entire sequence is from Macaca or if only the CDRs are or if only the frameworks are from Macaca origin.

c. Claim 1 and those dependent on claim 1 is indefinite for reciting "similar unique binding properties" because it is unclear what the phrase means. Does the phrase mean similar affinity, avidity, binding to the same antigen, or some other "binding property"?

d. Claim 5 is indefinite for reciting "sequences have an identity of at least 84%" because it is unclear if the term "sequences" is directed to the CDRs or to the entire light and heavy chain of the antibody in claim 1.

e. Claims 11-14 are indefinite for reciting "changed" because it is unclear how the antibody has been "changed". Has the amino acid sequence been altered or has the antibody been labeled, conjugated, has the nucleotide sequence been altered, or some other alteration?

f. Claim 15 is indefinite for it is not clear what the "other binding structures" are or if they bind the same antigen as the unlabeled antibody. In addition, it is unclear what other binding structures having other binding specificities means. Does the "other binding structures" bind the same antigen as the labeled and unlabeled antibody?

g. Claim 1 and those dependent on claim 1 is indefinite for reciting "subpopulation of normal human gastrointestinal epithelial cells" because it is not clear what the subpopulation is or if it means only under some conditions such as how the cells were treated or prepared such as lysis, etc..

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1-6, 16 are rejected under 35 U.S.C. ' 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-6, 16, as written, do not sufficiently distinguish over antibodies as they exists naturally because claims do not particularly point out any non-naturally occurring differences between the claimed antibodies and the structure of naturally occurring antibodies because claim 1 recites "binding structures with similar unique binding" and this reads on any antibody from any origin that binds the tumor cells.

In the absence of the hand of man, the naturally occurring antibodies are considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1966)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F.Supp 68 (1967), 155 USPQ 139, (District Court, New Jersey, 1967)). Amendment of the claims to recite "an isolated" or "purified" antibody or similar language would obviate this rejection.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 34, 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising the antibody of claim 1 which binds human gastrointestinal epithelial tumor cells and a subpopulation of normal human gastrointestinal epithelial cells or wherein the antigen is α6β4 or wherein the antibody has the six CDRs recited in claim 1, does not reasonably provide enablement for any pharmaceutical composition or any vaccine comprising the antibody of claim 1 which binds human gastrointestinal epithelial tumor cells and a subpopulation of normal human gastrointestinal epithelial cells or wherein the antigen is α6β4 or wherein the antibody has the six CDRs recited in claim 1 or has CDR sequences of at least 84% to sequences of human origin. The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to pharmaceutical or vaccine compositions as well as antibodies that have sequence that are 85% to those of the CDRs recited in claim 1.

The specification teaches in vitro data of detection of tumor cells using antibody A3 (see pages 19-32). The specification does not teach an in vivo detection or treatment or a vaccine method of using any antibody or any other antibody that had CDRs that are 85% identical to human sequences.

The specification provides no exemplification of or guidance on how to use the claimed vaccine formulation or antibody for activity immunotherapy in humans. The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very

optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1).

Furthermore, Boon (Adv Can Res, 1992, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). There is no indication in the specification that immunization with the antibody results in therapy against the tumor.

The claims as written as drawn to pharmaceutical compositions which read on in vivo treatment for cancer. However, the data presented to support the enablement of the claims is based on cell culture, in vitro studies.

One cannot extrapolate the teaching of the specification to the claimed invention because there is no guidance on or exemplification of any correlation between expression of the tumor antigen and increased risk of developing tumor progression *in*

vivo. The *in vitro* experimental data presented is clearly not drawn to subjects with tumor cells. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interations. Thus, based on the cell culture data

presented in the specification, it could not be predicted that, in the *in vivo* environment, expression of alpha6beta4 would be in any way correlated with increased risk of tumor progression.

Further, One cannot extrapolate the teaching of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para).

Claim 5 is broadly drawn to an antibody that has CDR sequences that are 85% identical to human sequences. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain

variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies as defined by the claims which may contain alterations in the CDRs, have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1, 2, 7, 8, 9, 34, 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Fernsten et al (Cancer Research 51:926-934, 1991, PTO-892, 5/20/04).

The claims are summarized as an antibody that binds human gastrointestinal epithelial tumor cells and a subpopulation of normal human gastrointestinal epithelial cells which is phage selected, derivatized by conjugation to a cytotoxic agent or a biologically active molecule, and compositions comprising such. Because of the indefinite nature of claim 1 it is interpreted to mean any antibody that binds human gastrointestinal epithelial tumor cells and a subpopulation of normal human gastrointestinal epithelial cells.

Fernsten et al teach an antibody that binds human gastrointestinal epithelial tumor cells and normal human gastrointestinal epithelial cells (see abstract and page 928) and the antibody is conjugated to horseradish peroxidase or 125I and compositions comprising such (see pages 927 and 928). Because of the indefinite nature of the claims the antibody of Fernsten et al meets the limitations if the claims because the antigen is in human gastrointestinal epithelial tumor cells and normal human gastrointestinal epithelial cells because the normal cells were cell lines and normal adjacent tissue which would be a subpopulation.

With regard to claim 2, which recites the antibody which is phage selected, the method in which the antibodies were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is

unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

13. Claims 1-2, 7, 16, 34, 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Quaranta et al (US Patent 5,320,942, issued 6/1994).
Claims 1-2, 7-9, 34, 37 have been described supra. Claim 16 recites wherein the binding structure recognizes a non-reduced form of α6β4. Because of the indefinite nature of claim 1 it is interpreted to mean any antibody that binds human gastrointestinal epithelial tumor cells and a subpopulation of normal human gastrointestinal epithelial cells.

Quaranta et al teach an antibody that binds α6β4 in cells under non-reducing conditions (see Table 4) and the antibody is labeled with a detectable label and compositions comprising the antibody. Because of the indefinite nature of the claims the art of Quaranta et al reads on the claims because it would be an inherent feature of the antibody to bind to human gastrointestinal epithelial tumor cells and a subpopulation of normal human gastrointestinal epithelial cells because the antibody binds the same antigen as claimed.

With regard to claim 2, which recites the antibody which is phage selected, the method in which the antibodies were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a

product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-2, 4-15, 34, 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fernsten et al (Cancer Research 51:926-934, 1991) as applied to claims 1-2, 7-9, 34, 37 above, and further in view of Queen et al (US Patent 6,180,370, filed 6/1995).

Claims 1-2, 7-9, 34, 37 have been described supra. Claims 4-6, 10-15 recite a derivative which is human origin, sequences of at least 85% to human origin (being interpreted as frameworks), low immunocinicity in humans, decreased avidity, changed to influence pharmacokinetic properties, labeled and is not inhibited by the same unlabeled antibody, conjugated to an immune activating molecule, increased yield.

Fernsten et al has been described supra. Fernsten et al does not teach a humanized antibody, decreased avidity, altered to influence pharma properties, or labeled and not inhibited by unlabeled antibody, conjugated to immune activating molecule, increased yield of the antibody. These deficiencies are made up for in the teachings of Queen et al.

Queen et al teach humanized antibodies which are non-immunogenic in humans and fragments thereof and the antibodies are low immunogenicity in humans and methods of producing such antibodies from hybridomas and the frameworks are human frameworks (which means they are 100% identical to human origin). Queen et la also

teach conjugation of cytotoxic as well as labels to the antibodies and enhanced immune response and vectors to produce high yield antibodies.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have humanized the antibody of Fernsten et al by the method of Queen et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have humanized the antibody of Fernsten et al by the method of Queen et al because Fernsten et al teach the antibody is useful for detection of human colon tumors and the antigen may be useful as a target for diagnosis and therapy (see page 933). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have humanized the antibody of Fernsten et al by the method of Queen et al because Queen et al teach humanization of antibodies that are directed to human antigens for treatment and diagnosis in humans and the antibodies use human frameworks and are less immunogenic in humans. It would have been obvious that fragments of the antibody as taught by Queen would be have altered pharmacokinetic properties because it was well known in the art at the time of the claimed invention that fragments of antibodies have altered half-lives as compared to entire immunoglobulins. In addition, it would have been obvious that the labeled antibody is inhibited by a unlabeled form because it is well known in the art that one would want a labeled antibody to bind just as well as the unlabeled antibody so that the label does not interfere with binding to the antigen.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

16. Claims 1-2, 4-16, 34, 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quaranta et al (US Patent 5,320,942) as applied to claims 1-2, 7, 16, 34, 37 above, and further in view of Queen et al (US Patent 6,180,370, filed 6/1995).

The claims have been described supra.

Quaranta et al has been described supra. Quaranta et al does not teach a humanized antibody, decreased avidity, altered to influence pharma properties, or labeled and not inhibited by unlabeled antibody, conjugate to immune activating molecule, increased yield. These deficiencies are made up for in the teachings of Queen et al.

Queen et al has been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have humanized the antibody of Quaranta et al by the method of Queen et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have humanized the antibody of Quaranta et al by the method of Queen et al because Quaranta et al teach the antibody is useful for detection of human tumors and used for diagnosis of human tumors (see column 33-34). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have humanized the antibody of Quaranta et al by

the method of Queen et al because Queen et al teach humanization of antibodies that are directed to human antigens for treatment and diagnosis in humans and the antibodies use human frameworks and are less immunogenic in humans. It would have been obvious that fragments of the antibody as taught by Queen would be have altered pharmacokinetic properties because it was well known in the art at the time of the claimed invention that fragments of antibodies have altered half-lives as compared to entire immunoglobulins. In addition, it would have been obvious that the labeled antibody is inhibited by a unlabeled form because it is well known in the art that one would want a labeled antibody to bind just as well as the unlabeled antibody so that the label does not interfere with binding to the antigen.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

17. Claims 1-9, 11, 14-16, 34, 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quaranta et al (US Patent 5,320,942) as applied to claims 1-2, 7, 16, 34, 37 above, and further in view of Anderson et al (US Patent 6,113,898 , filed 6/1995).

Claims 1-2, 4-9, 11, 14-16, 34, 37 have been described supra. Claim 3 recites wherein the sequences are of Macaca fascicularis origin. Due to the indefinite nature of the claims the claims are interpreted as being an antibody that binds α6β4 which is on human gastrointestinal epithelial cells and a subpopulation of normal gastrointestinal epithelial cells and the sequences are of Macaca origin.

Quaranta et al has been described supra. Quaranta et al does not teach an antibody that is of Macaca origin, conjugates, fragments. This deficiency is made up for in the teachings of Anderson et al.

Anderson et al teach production of antibodies in Macaca which are less immunogenic in humans and conjugates and fragments of the antibodies (see column 6-7, 16) and the antibodies have human constant regions. Because the constant regions are human they would be at least 85% to human sequences and would be of human origin (see instant claims 4-5).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a primatized antibody directed against the antigen of Quaranta et al by the method of Anderson et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a primatized antibody directed against the antigen of Quaranta et al by the method of Anderson et al because Quaranta et al teach the antibody is useful for detection of human tumors and used for diagnosis of human tumors (see column 33-34). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a primatized antibody directed against the antigen of Quaranta et al by the method of Anderson et al because Quaranta et al teach primatized antibodies are antigenically rejected upon administration to humans and they have long serum life and the sequences are 85-98% homologous to human antibodies (see column 7, lines 25-65). It would have been obvious that fragments of the antibody as taught by Anderson

et al would also have altered pharmacokinetic properties because it was well known in the art at the time of the claimed invention that fragments of antibodies have altered half-lives as compared to entire immunoglobulins. In addition, it would have been obvious that the labeled antibody is inhibited by a unlabeled form because it is well known in the art that one would want a labeled antibody to bind just as well as the unlabeled antibody so that the label does not interfere with binding to the antigen.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Siew, can be reached at (571) 272-0787.

20. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette,

1096 OG 30 (November 15, 1989). The Fax Center telephone number is 703-872-9306.

Larry R. Helms

571-272-0832

LARRY R. HELMS, PH.D
PRIMARY EXAMINER